B4

5. **(Amended)** A method of claim 2, wherein said amplification step employs a primer pair selected from the group consisting of any of SEQ ID Nos. 1 and 2; 3 and 4; 5 and 6; 7 and 8; 9 and 10; 11 and 12; and 13 and 14.

REMARKS

The above amendments enter no new matter. Support for the amendment to the paragraph spanning lines 4-10 at page 88 can be found throughout the application, for example at page 8, lines 18-22. Support for the amendment to claim 1 can be found throughout the application, for example, at page 8, lines 6-34. Applicants expressly reserve the right to pursue without prejudice the originally filed claims as well as other disclosed subject matter at a latter date.

Applicants note that the Examiner has acknowledged Applicant's election with traverse of Group I. The Examiner states that claims 1-7 and 77-79 are under consideration. The objections and rejections set forth in the Office Action are addressed below in the order in which they are raised. This response is identical to that issued by Applicants on March 19, 2002, except for the addition of a formal traversal of the instant nonstatutory double patenting rejection.

Priority

The Office Action states that, should Applicants desire the benefit of priority to application U.S. 09/431,352, specific reference to the earlier filed application must be made in the instant application. Accordingly, the specification has been amended above so as to insert a claim to the benefit of U.S. 09/431,352, and an incorporation by reference of the contents of this application, as the first sentence of the application following the title.

Specification

The specification has been objected to as containing certain remaining nucleotide and/or amino acid sequences disclosures, encompassed by definitions set forth in 37 CFR 1.821(a)(1) and (a)(2), that are not yet in compliance with 37 CFR 1.821-1.825 which require submission of a CRF and paper copy of the Sequence Listing, an amendment directing the

entry of the Sequence Listing into the specification and a letter stating that the content of the paper and computer readable copies are the same. Accordingly, these requirements have been satisfied by the accompanying enclosures and instructions for insertion of the Sequence Listing provided with this response.

Informalities

The disclosure is objected to because of the duplication of the phrase "and 13" in claim 5, line 3. Accordingly, Applicants have removed this duplicated term by the accompanying amendment.

REJECTIONS

Rejections Under 35 U.S.C. §112, first paragraph-Enablement

The Office Action states that claims 1-7 and 77-79 have been rejected under 35 U.S.C. § 112, first paragraph, because "the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claims." The Office Action states that "the specification teaches that the IL-1RN(VNTR) allele 2 is associated with a lower restenosis rate in patients with SVD," however the Office Action proceeds to critically critique and criticize this observed association using the Applicants own data. For example, the Office Action claims that certain reported data (e.g. that obtained with a population of "MVD patients") are inconsistent with the claimed association. Applicants traverse this rejection for the reasons which follow.

First, Applicants have taught that susceptibility to restenosis is a complex trait related to the general processes of wound healing (see page 2, lines 21-26) and which involves many genes in addition to IL-1 such as ELAM-1, ICAM-1 as well as TNFa, lymphotoxin, bacterial endotoxins, prostaglandin E2 (PGE2), bFGF and TGFα and TGFβ and MDGF (see page 2, line 30 - page 3, line 15). Accordingly, genetic variation at multiple loci, in addition to variation at IL-1, may contribute to susceptibility to restenosis. It is widely appreciated in the art that statistical associations between polygenic traits and single contributory genetic

polymorphisms requires an adequate sample population size and/or limited genetic diversity. Accordingly, the failure to find a statistically demonstrable association in one study of, e.g. limited sample size, is not determinative. Indeed, the invention makes no claims to a distinction in sample population between the so-called "SVD" sample study and the "MVD" study, despite inferences by the Examiner to the contrary. Rather the invention provides statistical evidence, adequate to the person of skill in the art, that there is an association between genetic variation at the IL-1 locus and the risk for restenosis. The fact that the Examiner has not found the results of all the exemplary studies to her liking is not determinative to a finding of lack of enablement. Indeed, case law has established that working examples need not necessarily even be present to establish enablement. *See in re Wrtght*, 999 F.2d 1557, 1561 (Fed. Cir. 1993) ("Nothing more than objective enablement is required and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples"); *In re Robins*, 429 F.2d 452 (C.C.P.A. 1970) (stating that "representative [samples} are not required by the statute and are not an end in themselves.") Rather the relevant inquiry is whether the disclosure would provide adequate guidance to one of skill in the art to make and use the claimed invention. Applicants assert that one of skill in the art could readily make and use the claimed invention of IL-1 polymorphism-based genetic testing for a predisposition to restenosis based upon the working examples and further guidance provided by in the application.

Second, the Office Action states that "the specification has not provided any specific data clearly establishing the occurrence of IL-1b (-511), IL-1b(+3954), IL-1b (+4845) alleles in restenosis and no working examples are provided in the specification in which these alleles have been successfully employed to determine the presence or predisposition to restenosis." In response, Applicants note that the absence of a specific working example, as noted above, is not determinative to a finding of lack of enablement. Rather, the proper inquiry is whether one of skill in the art would have been able to practice the claimed invention (e.g. use of IL-1b (-511), IL-1b(+3954), IL-1b (+4845) polymorphic alleles to predict restenosis susceptibility) without undue experimentation. Applicants assert that one of skill in the art could readily make and use this breadth of the claimed invention based upon the working examples and further guidance provided by in the application. Indeed, the application teaches the association of the subject polymorphisms in characteristic haplotypes, and the skilled

artisan would appreciate that, where an individual allele of a haplotype is associated with restenosis, other alleles of the same haplotype are also indicative. Indeed, recent exemplary genome-wide linkage disequilibrium studies (see Exhibit A; Johnson et al. (2001) Nature Genetics 29: 233-7) have demonstrated that characteristic SNPs that "tag" a given haplotype may be used to reduce genotyping required to identify characteristic disease-associated haplotypes. Accordingly, reconsideration and removal of this rejection is respectfully requested.

Rejection Under 35 U.S.C. §112, second paragraph

The Office Action states that claims 1-7 and 77-79 have been rejected as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, the Office Action states that the subject claims are indefinite for "failing to recite a final process step which agrees back with the preamble." In an effort to expedite prosecution, and not in acquiescence to this rejection, Applicants have amended subject independent claim 1 to remove the term "arterial" so that the preamble (i.e. "A method for determining whether a subject has or is predisposed to developing an restenosis") agrees back to the final process step (i.e. "wherein detection of the restenosis allele indicates that the subject has or is predisposed to the development of a restenosis"). Accordingly, the amendment has obviated the grounds for this rejection and reconsideration and removal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. §102(e)

The Office Action states that claims 1, 3, 4, 6 and 7 have been rejected under 35 U.S.C. 102(e) as being anticipated by Bray et al. (U.S. Patent No. 5,955,266). Applicants traverse this rejection in light of the proposed clarifying amendment to independent claim 1 specifying that the claim relate to "a restenosis associated IL-1 allele." In contrast, Bray does not teach an IL-1 associated allele. Rather, Bray teaches a GPIIIa gene polymorphism (i.e. the PI^{A2} polymorphism) that is associated with thrombotic disease. In order to for a reference to anticipate a claimed invention, the reference must teach each and every element of the claimed invention. As Bray fails to teach an IL-1 allele associated with restenosis, it fails to anticipate amended independent claim 1 and, necessarily, dependent claims 3, 4, 6 and 7. Accordingly, reconsideration and removal of this rejection is respectfully requested.

Double Patenting

The Office Action states that claims 1, 3, 4, 6 and 7 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,268,142. Furthermore, the Office Action states that claims 1-7 and 77-79 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6,210,877; and that claims 1-7 and 77-79 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 2-4 and 6-13 of copending Application No. 09/431,352. The Office Action further points out that these rejection may be obviated by the filing of terminal disclaimer in compliance with 37 CFR 1.32(c) where common ownership can be shown pursuant to 37 CFR 1.130(b).

Applicants respectfully formally traverse the obviousness-type double patenting of the instant pending claims 1-7 and 77-79 over claims 1-15 of U.S. Patent No. 6,210,877 as it is Applicants' belief that the pending claims are of distinct scope from the cited issued claims. In particular, Applicants note that the claims in U.S. Patent No. 6,210,877 are directed to distinct subject matter (i.e. prediction of coronary artery disease as opposed to restenosis) utilizing distinct alleles of IL-1. With respect to the pending obviousness-type double patenting rejection of claims 1, 3, 4, 6 and 7 over claims 1-6 of U.S. Patent No. 6,268,142, Applicants state that, solely in an effort to expedite prosecution and not in acquiescence to the rejection, they will file a terminal disclaimer should the instant pending claims be found allowable. With respect to the provisional obviousness-type double patenting rejection of claims 1-7 and 77-79 in view of claims 2-4 and 6-13 of copending Application No. 09/431,352, Applicants formally traverse the rejection inasmuch as the cited copending claims of Application No. 09/431,352 have been canceled by Applicants' last-filed Response under 37 CFR § 113 and pending new claims 41-58 are drawn to distinct subject matter.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims now pending are in condition for allowance, and notification of such is respectfully requested. If for any reason a telephonic conference with the Applicant would be helpful in expediting prosecution of the instant application, the Examiner is invited to call Applicants' Agent at (617) 832-1764.

If there are any other fees due in connection with the filing of this Response, please charge the fees to our Deposit Account No. 06-1448.

Respectfully submitted,
FOLEY, HOAG, & ELIOT

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MARKED-UP VERSION OF AMENDMENTS TO CLAIMS UNDER CONSIDERATION

WHAT IS CLAIMED IS:

1. **(Amended)** A method for determining whether a subject has or is predisposed to developing [an arterial] restenosis, comprising detecting a restenosis associated IL-1 allele in a nucleic acid sample from the subject, wherein detection of the restenosis allele indicates that the subject has or is predisposed to the development of [a] restenosis.

2. A method of claim 1, wherein the restenosis allele is selected from the group consisting of allele 1 of any of the following markers: IL-1A (+4845), IL-1B (-511), IL-1B (+3954) and IL-1RN (+2018) or an allele in linkage disequilibrium therewith.

3. A method of claim 1, wherein said detecting step is selected from the group consisting of:

a) allele specific oligonucleotide hybridization;
b) size analysis;
c) sequencing;
d) hybridization;
e) 5' nuclease digestion;
f) single-stranded conformation polymorphism;
g) allele specific hybridization;
h) primer specific extension; and
j) oligonucleotide ligation assay.

4. A method of claim 1, wherein prior to or in conjunction with detection, the nucleic acid sample is subject to an amplification step.

5. **(Amended)** A method of claim 2, wherein said amplification step employs a primer pair selected from the group consisting of any of SEQ ID Nos. 1 and 2; 3 and 4; 5 and 6; 7 and 8; 9 and 10; 11 and 12; and 13 [and 13] and 14.

6. A method of claim 3, wherein said size analysis is preceded by a restriction enzyme digestion.

MARKED-UP VERSION OF AMENDMENTS TO SPECIFICATION

The paragraph appearing at lines 4-10 on page 88 was amended as follows:

Results: Typing of additional numbers of individuals is required to bring the results to significance, but preliminary results indicate that allele 1 [2] of the 4845, -511, +3954 and VNTR markers in the IL-1RN gene will be over-represented in restenosis. It is predicted that individuals with at least one copy of allele 1 [2] from one of the above markers are more likely to have restenosis than those who are negative for allele 1 [2]. Individuals who are homozygous for any of these alleles, or have allele 1 [2] from more than one marker are estimated to have even higher risk for restenosis.